

AMENDMENTS TO THE DRAWINGS

The attached sheets of drawings include changes to Fig. 1 and 2. These sheets replace the original sheets including Figures 1 and 2. The lines in Figures 1 and 2 have been clarified. In Figure 2, line and symbol colors were changed to black and symbols were enlarged.

Attachment: Replacement sheets (2)

REMARKS

After entry of this amendment, claims 1-6 and 8-27 are pending, of which claims 1-6 and 11-20 are withdrawn. The claims are amended without prejudice to or disclaimer of Applicants' right to pursue the cancelled subject matter in a later application. Claim 7 is cancelled without prejudice or disclaimer and is rewritten in independent form as new claim 27. New claim 27 finds support in original claims 1, 5, and 7. Claims 8, 9, and 21 have been amended for proper dependency. The amendments to claim 22 find support *inter alia* in the original claims and in the specification, for example, at page 13, lines 4-11. No new matter has been added.

The specification has been amended to include headings and a brief description of the figures, which finds support in the specification at page 31, lines 9-23. No new matter has been added.

Election/Restriction

Applicants thank the Examiner for rejoining and examining claims 7-10 with the claims of Group III.

Applicants wish to correct an obvious typographical error in the Response to Restriction Requirement dated November 13, 2007. On page 2 of the Response, the sentence starting at line 10 should read "Kumiyoshi *et al.* (D1 in the International Preliminary Report on Patentability (IPRP)) does not teach or disclose such a method as noted in the IPRP." The error was an inadvertent omission as clearly indicated in the IPRP and in the sentence following it, *i.e.* "Therefore, Kumiyoshi does not disclose the method of the invention as claimed." Applicants request that the correction be made of record.

Rejections under 35 U.S.C. § 112

Written Description Rejection

Claims 7-10 and 21-26 were rejected under 35 USC §112, first paragraph, for allegedly failing to comply with the written description requirement. Applicants respectfully traverse.

The Examiner requires correction of the claims for S-enantioselectivity. Applicants submit that claim 5 from which claim 7 depends already recites that the reducing agent or catalyst "exhibit selectivity with regard to the formation of (S)-3-methylamino-1-(thien-2-yl)propan-1-ol." However, to expedite prosecution, the claims have been amended and/or rewritten in independent form without prejudice or disclaimer. Because the claims already recited selectivity with regard to the formation of (S)-3-methylamino-1-(thien-2-yl)propan-1-ol and further in light of the amendments, reconsideration and withdrawal of the rejection is respectfully requested.

Indefiniteness Rejection

Claims 7-10 and 21-26 were rejected under 35 USC §112, second paragraph, as being indefinite. Specifically, claim 7 was rejected as being dependent from a non-elected claim. Claim 7 was also rejected for reciting an E.C. number. Claim 7 has been rewritten in independent form as new claim 27 and claim 7 has accordingly been cancelled without disclaimer or prejudice. The rejection is believed to be rendered moot. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim 22 was rejected for reciting only a step of making an intermediate. Claim 22 has been amended without prejudice or disclaimer to better conform to U.S. practice. In light of the amendment, the rejection is believed to be rendered moot. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim 8 was rejected for reciting E.C. numbers. Claim 8 have been amended without disclaimer or prejudice. In light of the amendments, the rejection is rendered moot. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim 23 was rejected for reciting "without being isolated" based on its dependency from claim 21, which depends from claim 7, which depends from claim 1. The dependency of claim 21 has been amended without prejudice or disclaimer. In light of the change of dependency of claim 21, the rejection is believed to be rendered moot. Reconsideration and withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 7-10 and 21-26 were rejected under 35 U.S.C. § 103(a) as being obvious over Kuniyoshi *et al.* (JP2003192681; hereinafter “Kuniyoshi”) and Dieter *et al.* (DE10248479; hereinafter “Dieter”), individually, in view of Wheeler *et al.* (hereinafter “Wheeler”) and Hummel. Applicants respectfully traverse and request reconsideration in view of the following remarks.

Applicants submit herewith a certified copy of the English translation of the priority document DE 103 45 772.0 filed October 1, 2003, accompanied by a statement that the translation of the certified copy is accurate, pursuant to 37 CFR § 1.55 (a)(4)(i)(b) and (a)(4)(ii). Applicants respectfully request that this certified translation be made of record.

Please note that the country of the priority document and filing date is incorrect in PAIR and on the filing receipt. Applicants had previously submitted a Request for Corrected Filing Receipt on February 8, 2007; however, the corrections have still not been entered. The correct date and country of the priority document were correctly indicated in the Application Data Sheet and the Declaration submitted with the initial national stage filing of this application. Applicants are submitting a Second Request for Corrected Filing Receipt with the filing of this response. Correction is respectfully requested.

The priority date of the present application is October 1, 2003. Dieter has a publication date of 2004. Therefore, Dieter is not prior art because the publication date is after the filing date of the priority application to which the present application claims benefit. In view of the submission of the certified English translation of the priority document, the rejections as to the Dieter reference are believed to be rendered moot. Reconsideration and withdrawal of this rejection is respectfully requested.

The examiner bears the initial burden of establishing *prima facie* obviousness. See *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993).

The Examiner asserts that Kuniyoshi teaches a process of making 3-methylamino-1-(thienyl-2-yl)propan-1-ol. The process disclosed in Kuniyoshi is different than the process from the present application. The process disclosed in Kuniyoshi provides for a fully chemical way of

producing said compound, which does not teach or suggest the use of a hydrogen halide or an enzyme, as also acknowledged by the Examiner. In the Kuniyoshi process, thiophene is reacted with 3-chloropropionic acid chloride in the presence of a Friedel-Crafts catalyst to provide 1-(2-thienyl)-3-chloropropene-1-one. This propanone is *chemically reduced* in a subsequent step in the presence of hydrogen and a suitable asymmetric hydrogenation catalyst containing a transition metal. The chlorinated propanole intermediate is subsequently aminated in the presence of methylamine. In contrast, the present claimed invention relates to a process for preparing the S-enantiomer of formula I-S comprising a combination of a first chemical step directed to the preparation of the achiral propanone corresponding to formula III and a second *enzymatic* step, which stereoselectively converts the propanone to form a chiral intermediate compound of formula IV, which is then chemically converted to the final amine of formula I-S. Kuniyoshi does not teach or suggest an enzymatic step or that the asymmetric hydrogenation catalyst containing a transition metal could be replaced by an enzyme. Additionally, Kuniyoshi does not teach or suggest treating the reaction mixture containing propanone with a halogen halide before the next step of conversion of propanone to the alcohol is performed as required by the claims.

The Examiner relies on Wheeler for allegedly teaching a process of making 3-methylamino-1-(thienyl-2-yl)propan-1-ol wherein HCl is used. However, the process disclosed in Wheeler teaches a different type of chemical reaction than the presently claimed process as explained in detail in the present specification at page 2 line 16 through page 3 line 18. In contrast to the present claimed invention, Wheeler suggests thiophene-2-carboxylic acid or thieneylchloride (see Wheeler, page 215, scheme II, compounds 3a, 3b, 3c, and 3d) as starting points for their synthesis, rather than the conversion of thiophene with a β -halopropionyl halide or an acryloyl halide as recited in the claims. Additionally, Wheeler teaches the formation of 1-(2-thienyl)2-propene-1-one in the first step of their process which formation is avoided in the present method by treatment with gaseous hydrogen halide (see specification at page 7, lines 1-2, 12-17) being passed in simultaneously or after the reaction has taken place, but before the reaction product is isolated. Wheeler further teaches the use of a liquid HCl/ether phase (see Wheeler, page 218, second full paragraph), in contrast to the presently claimed process where gaseous hydrogen halide is being passed.

The Examiner relies on Hummel for allegedly teaching a dehydrogenase and source of dehydrogenase for R- and/or S-enantioselective process of making alcohols from ketones, referring to pages 148-150 as teaching the prerequisite dehydrogenase procedure. Applicants strongly disagree. In the passage referred to by the Examiner, in which three enzymes from baker's yeast were isolated of which two were (R)- and one was (S)-specific, Hummel teaches that "[t]he substrate specificity of these enzymes shows that in increasing the chain length in the ketone led to contrary reaction rates of the three enzymes, thus producing often a mixture of isomers. Therefore it is not possible to predict the stereospecificity of a reaction using a new substrate . . ." (see Hummel page 149). The Examiner further points to Tables 5 and 6 for examples of substrates. The substrate of the present invention is not disclosed in Hummel. Tables 5 and 6 do not teach or suggest that an alcohol dehydrogenase may be applicable to catalyse the stereospecific synthesis of the substrate of the present claims (*i.e.* a secondary aliphatic monoalcohol which is substituted on one terminal end with a heterocyclic 5-membered sulphur-containing ring substituent and which carries on the other end of the carbohydrate chain a halogen). As stated above, Hummel specifically teaches that it is not possible to predict stereospecificity of a reaction using a new substrate. Thus, Hummel does not teach or suggest that a dehydrogenase would be applicable or have a reasonable expectation of success for stereoselective synthesis of a compound of formula I-S.

"[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007) quoting *In re Kahn*, 441 F.3d 977, 988, (Fed. Cir. 2006). Furthermore, the Examiner cannot selectively pick and choose from the disclosed parameters without proper motivation as to a particular selection. The mere fact that a reference may be modified to reflect features of the claimed invention does not make the modification, and hence the claimed invention, obvious unless the prior art suggested the desirability of such modification. *In re Mills*, 916 F.2d 680, 682, 16 USPQ2d 1430 (Fed. Cir. 1990); 16 *In re Frutch*, 23 USPQ2d 1780 (Fed. Cir. 1992). Thus, it is impermissible to simply engage in a hindsight reconstruction of the claimed invention where the reference itself provides no teaching as to why the applicant's combination would have been obvious. *In re Gorman*, 933 F.2d 982, 987, 18 USPQ2d 1885,

1888 (Fed. Cir. 1991). A reasonable expectation of success must be established for a proposed combination of references to render claims *prima facie* obvious. See MPEP § 2143.02 (citing *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)). The teaching or suggestion to make the combination and the reasonable expectation of success must both be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

The Examiner argues that one of ordinary skill in the art would have known to use hydrogen halide and DH in the process of Kuniyoshi and would be motivated to do so based on the teaching of the references. Applicants respectfully disagree. This alleged motivation lacks specificity to support a legal conclusion of obviousness. See *KSR*, 127 S. Ct. at 1741 (holding that “there must be some articulated reasoning with some rational underpinning to support a legal conclusion of obviousness.”). *KSR* still requires some reason one would have combined Kuniyoshi, Wheeler, and Hummel. *Id.* (holding that “a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. . . it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.”) (emphasis added). A statement that modifications of the prior art to meet the claimed invention would have been “well within the ordinary skill of the art at the time the claimed invention was made” because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). See MPEP § 2143.01 IV. Simply stating that the motivation is in the teaching of the references does not provide a reason that would have prompted a person of ordinary skill in the relevant field to combine the process of Kuniyoshi which uses an entirely chemical process without hydrogen halide and without an enzyme with the teaching of a different reaction using different starting materials as in Wheeler and with the teaching of dehydrogenases described as being unpredictable in their reactivity with new substrates and disclosing substrates other than that presently claimed as disclosed in Hummel. Such a statement lacks the specificity required to support a legal conclusion of obviousness and is thus insufficient to establish *prima facie* obviousness.

The Examiner further asserts several alternatives for allegedly finding obviousness. The Examiner alleges that “it would have been obvious to try hydrogen halide and DH in the process of Kuniyoshi” (see Office Action at page 5); that the process claimed “are not applicant’s invention. Applicant has done no more than combine well know inventions” (see Office Action at page 5); that “applicant has done nothing more than substitute hydrogen halide and DH in the process of Kuniyoshi” (see Office Action at page 6); and that “given the teaching of the prior arts, one of ordinary skill in the art faced with the need to make 3-methylamino-1-(thienyl-2-yl)propan-1-ol would have known to use hydrogen halide and DH at the time the invention was made” (see Office Action at page 6). However, the Examiner has failed to provide any explanation, rationale, or suggestion in the references cited for why it would be obvious to try, why it would be obvious to combine, why it would be obvious to substitute compounds, what compounds would be substituted or why one skilled in the art would have known to use the compounds in the claimed process. Simply quoting passages from *KSR* does not provide explanations or rationale for these assertions as is required under *KSR*. Such statements lack the specificity required to support a legal conclusion of obviousness and are thus insufficient to establish *prima facie* obviousness.

Moreover, it is well established that under 35 U.S.C. § 103 the Examiner must consider the reference as a whole, including portions that teach away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); see also *KSR*, 127 S. Ct. at 1740. The process of Kuniyoshi uses a stereoselective hydrogenation catalyst containing a transition metal in contrast to the enzyme of the present claims. Kuniyoshi characterizes the stereoselective hydrogenation catalyst containing a transition metal as an “indispensable ingredient” (see paragraph [0017] at page 5 of the computer generated translation of Kuniyoshi, herein attached for the Examiner’s convenience). Thus, Kuniyoshi suggests that the stereoselective hydrogenation catalyst containing a transition metal is essential for their process to work and thus cannot be substituted. Kuniyoshi therefore teaches away from a combination with Hummel. Moreover, a reasonable expectation of success must be established for a proposed combination of references to render claims *prima facie* obvious. See MPEP § 2143.02 (citing *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)). Assuming *arguendo* Kuniyoshi and Hummel were

combinable, there would be no expectation of success since Kuniyoshi teaches that the stereoselective hydrogenation catalyst containing a transition metal is essential and the Examiner has further not provided any basis for such a modification.

Additionally, Hummel, as explained above, discloses that it is not possible to predict stereospecificity of a reaction with a dehydrogenase using a new substrate. Since the substrate of the present process is not disclosed in Hummel, the dehydrogenase process disclosed in Hummel would be inapplicable to the substrate of the present process. As quoted by the Examiner, *KSR* held that substitution of known elements or combinations of familiar elements must yield predictable results for a finding of obviousness. See also MPEP § 2143 (If any of the findings cannot be made (*i.e.* the substitution of one known element for another yielding predictable results to one of ordinary skill in the art), then the rationale on which the Examiner based the obviousness rejection cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art). As mentioned above, since Kuniyoshi discloses that the stereoselective hydrogenation catalyst containing a transition metal is essential and Hummel discloses unpredictability for substitutions of substrates, both Kuniyoshi and Hummel teach away from any substitution or combination. Assuming *arguendo* Kuniyoshi and Hummel were combinable, the results would not be predictable as taught by Hummel, which defeats a finding of obviousness. See *KSR* and MPEP § 2143.

Furthermore, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references normally do not render the claims obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959) (The court reversed the obviousness rejection holding the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." 270 F.2d at 813, 123 USPQ at 352.). MPEP § 2143.02 VI. The proposed modification to Kuniyoshi suggested by the Examiner requires a "substantial reconstruction and redesign" of elements and changes the principle under which Kuniyoshi operates from a process where the use of a stereoselective hydrogenation catalyst containing a transition metal is indispensable to a process that does not require such a catalyst. Further Kuniyoshi provides no motivation for such a substitution. Moreover, Hummel discloses

unpredictability for substitutions of substrates and thus also provides no motivation or any reasonable expectation of success for substituting substrates or for substituting a stereoselective hydrogenation catalyst containing a transition metal for an enzyme. Introducing the enzyme from Hummel into the process of Kuniyoshi would change the basic principle under which the Kuniyoshi process was designed to operate. Thus, Kuniyoshi and Hummel are not combinable for this additional reason.

The Examiner further alleges that the source, the gene, and the E.C. numbers are not limitations under U.S. patent practice. Applicants strongly disagree. Genes have long been patentable since at least the 1980's as evidenced by the Supreme Court decision of *Diamond v. Chakrabarty*, 447 U.S. 303 (1980). See also MPEP § 2400 on Biotechnology.

For at least these reasons, Kuniyoshi, Wheeler, and Hummel, alone or in combination, do not render obvious the subject matter of the independent claims or the claims dependent therefrom. See *In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988) (holding that if an independent claim is nonobvious then any claim dependent therefrom is nonobvious).

Reconsideration and withdrawal of the rejection is respectfully requested.

Double Patenting Rejection

Claims 7-11 and 21-26 are provisionally rejected for non-statutory obviousness-type double patenting over Application No. 10/552,218 (the '218 application). The Examiner is directed to the Image File Wrapper of the '218 application, which indicates that the status of the '218 application is "Abandoned." Accordingly, a double patenting rejection is not appropriate. Reconsideration and withdrawal of the rejection is respectfully requested.

Objections To The Specification and Figures

The Examiner indicated that the lines in Figures 1, 2A and 2B are not clear and that the specification does not have sub-headings. Applicants attach herewith replacement sheets for Figures 1, 2A and 2B. Furthermore, the specification has been amended to include sub-headings and a Brief Description of the Figures. In light of the amendments and replacement sheets,

reconsideration and withdrawal of the objections to the specification and figures are respectfully requested.

Information Disclosure Statement

On the Information Disclosure Statement, the Examiner cross-out three references indicating that they were not translated. A concise explanation of relevance of the three references is found in the specification. The Examiner is directed to the specification at page 3, lines 18-23, which discusses reference CI, and recites that "Thus, in CR Acad. Sci., Ser. C, 1979, 288 (1), 49-52, A. Etienne et al. describe the preparation of the chloropropanone III.1 by means of the Friedel-Crafts reaction of thiophene with 3-chloropropionyl chloride in the presence of aluminum trichloride, as a Lewis acid catalyst, and in nitromethane as solvent. The chloropropanone III.1 is obtained in a yield of only 7%. . . ." Additionally, in the specification at page 9 line 45 through page 10 line 2, reference CK is discussed and recites "Suitable asymmetric borohydrides are described, for example, in E. J. Corey, C. J. Helal, Angew. Chem. 1998, 110, 2092-2118 or in M. M. Midland . . ." Furthermore, in the specification at page 14, lines 30-34, reference BC is discussed and recites "An immobilized enzyme is understood as meaning an enzyme which is fixed to an inert support. Suitable support materials, and the enzymes which are immobilized on them, are known from EP-A-1 149849, EP-A-1 069 183 and DE-OS 100193773, and also from the literature references which are cited therein." Applicants submit that these passages in the specification provide a concise explanation of references BC, CI and CK pursuant to 37 CFR § 1.98(a)(3)(i). Accordingly, Applicants respectfully request that these references be considered by the Examiner and that the references be made of record and appear among the "References Cited" on any patent to issue from this application.

CONCLUSION

In view of the amendments and the reasons presented above, reconsideration of the rejections and allowance of the claims is respectfully requested. If any outstanding issues remain, the Examiner is invited to telephone the undersigned at the number given below.

Accompanying this response is a petition for a three-month extension of time to and including June 12, 2008 to respond to the Office Action mailed December 12, 2007 with the

required fee authorization. No further fee is believed due. However, if any additional fee is due, the Director is hereby authorized to charge our Deposit Account No. 03-2775, under Order No. 13111-00035-US from which the undersigned is authorized to draw.

Respectfully submitted,

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